Remarks

The claims pending in this application are 1, 2, 4-27, 29 and 30. All claims stand rejected and/or objected to. Claims 1, 2, 5, 23-27, 29, and 30 are amended. New claims 31-34 are introduced, and appropriate fees (if required) are provided herewith for inclusion of these new claims.

I. Claim Objections

The Examiner has suggested that all claims in this application should be amended so that in each instance where "marker" is mentioned in the claims, it should be specified that this is an "olfactory marker" as defined in the specification, "so as to parallel Applicant's specification." This ground for objection has been carefully considered, and the entire specification has been carefully reviewed. As a result, Applicants urge that this ground for objection should be reconsidered and withdrawn. This is because, throughout, the specification makes it clear that what is of significance to this invention is that a marker is included in the medication the taking of which by a particular patient is to be confirmed. All that is required for this marker is that it is non-toxic and that it is detectable by one of a number of means described in detail in the specification. Odorous markers and olfactory markers are but examples of the class of compounds that may be used for this purpose. Thus, for example, the Abstract of the disclosure states: "markers, **such as odors**", making it clear that markers may be other than odors and that odors are merely exemplary markers. Further, the Abstract states "In the case of olfactory markers" again making it clear that there are other cases which fit the definition of marker beyond olfactory markers. Other support for the broad reading of the term "marker" may be found, for example, at the following locations in the disclosure:

Paragraph	Text
0003	"marker detection in the form of odors or the like…such markers are detectable either directly from the medication itself or from an additive combined with the medication"
0009	"detecting markers, such as odors…

0010	"it is an object of the present invention to detect marker substances as a measure of patient compliance …"
0017	"The detected markers are derived either directly from the medication itself or from a novel additive combined with the medication (referred to herein as "markers"). Such markers preferably **include** olfactory markers (odors) **as well as other substances and compounds which may be detectable** by various methods, as described in more detail herein."

While this is not an exhaustive listing of all locations in the specification which support a reading of markers which extends beyond olfactory or odorous markers, this table sufficiently supports the point. A complete reading of the specification consistently relates to use of markers which may or may not be olfactory markers or which may or may not be odors. It would be inappropriate, in light of this broad disclosure in the specification, to require that only compounds which could be considered to have an odor (presumably detectable by a nose) are useable as markers according to the present invention. Accordingly, except for new claim 34, the claims are not limited per the suggestion of the Examiner to "olfactory marker." Reconsideration and withdrawal of this ground for objection is respectfully requested.

II. Claim Rejections

1. 35 USC §112, ¶1

All claims stand rejected under 35 USC 112, first paragraph, because the specification, while acknowledged as "being enabling for providing a medication that itself comprises the detectable odorous marker," is said to fail to "reasonably provide enablement for providing a combination of a medication and an odorous maker so as to detect the present (sic presence)/absence of the odorous marker to indicate compliance/non-compliance in taking the medication." It is asserted that "the odorous marker must be a part of the medication, otherwise no positive connection with the odorous

marker can be made to the medication." As a result, it is the Office's position that the "currently recited method is not operable in detecting if the medication has/has not been taken as it only tests if the odorous marker has/has not been taken."

Applicants urge that this rejection is based on a definitional mis-apprehension, and that the rejection may readily be withdrawn upon recognition/acknowledgement that the application makes it plain that the term "medication" implies both the active pharmaceutical ingredient (the "API") and any excipients, markers, including but not limited to odorous or olfactory markers and the like. The foregoing table already provides evidence that the Office's position on this point cannot be correct – the Abstract of the disclosure states that the "markers result either directly from the medication itself or from an additive combined with the medication." See likewise, the above table, referencing disclosure at paragraph 0003, and 0017. Again, this cited disclosure is not the exclusive disclosure in the specification which makes it plain that the term "medication" includes the API, which itself may give rise to a detectable marker, or the marker may be a compound which is included with the API as part of "the medication." See also the legend of Figure 2, which states "PCMS includes marker compound included in medication that is exhaled into detection system for accurate and reliable monitoring off-site." See, likewise, the legend of Figure 3, which states: "Step 1 – Medication is taken, releasing Marker Compound." Likewise, for Figure 4, for which the legend states: "PCMS includes marker compound included in medication that is exhaled into detection system for accurate and reliable monitoring off-site." Thus, it is incorrect to state that the "currently recited method is not operable in detecting if the medication has/has not been taken as it only tests if the odorous marker has/has not been taken," as the marker is part of the medication. Reconsideration and withdrawal of this rejection is respectfully requested.

2. 35 USC §112, ¶2

All claims stand rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission assertedly "amounting to a gap between the elements." The basis for this rejection is the same as that addressed above in connection with the rejection under

35 USC 112, first paragraph, namely, the purported need to include in the medication an odorous marker. Applicants urge that this issue has been resolved above, and therefore this rejection may be withdrawn. It is noted, in any event, that the Examiner has conceded that claims 2, 9, and 10 as they stood prior to issuance of the outstanding Office Action contained the relevant limitation and therefore should not have been subject to this ground for rejection. Further, claim 1 is explicit in requiring "a combination of a medication and a marker." Reconsideration is requested.

3. 35 USC §112, ¶2

All claims stand rejected as being indefinite. The rejection was based on the use of the term "odorous markers" which was alleged to be unclear. However, in light of the review of the specification, as outlined above, Applicants assert that the claims which now reference "detectable marker" rather than "odorous markers" or "olfactory markers" are completely clear and definite and are supported by the specification. Reconsideration and withdrawal of this ground for rejection is therefore respectfully urged.

Regarding claim 5, the Office Action asserts it is "unclear how the recitation in claim 5 further limits the method of claim 1 (as well as claim 4)." Claim 5 is hereby amended to address this concern by making it clear that it does indeed limit both claims 1 and 4 from which it depends by further requiring that the sensor technology utilized in the claimed method produces a unique electronic fingerprint which is an indication of the presence of the marker in the patient's breath. While it is acknowledged that the Examiner believes that it is also necessary for the claim to recite a baseline or control odor response so as to not mischaracterize natural odors of the patient's breath not associated with the marker administered with the medication (the Examiner kindly references the pre-grant publication of US 2004/0081587, paragraphs 0030, 0031), Applicants respectfully note that such baseline or control odor response calibration is merely a preferred embodiment. However, it is also the case that this is not required for the method to be operative. For example, where the marker is one which is not present in the natural breath components of the patient, the mere presence or absence of the marker in the breath, as detected by the sensor technology, is sufficient for the

method to provide the compliance data required. This ground for rejection of claim 5 may therefore be withdrawn.

Also with respect to claim 5, it is asserted that there is insufficient antecedent basis for the limitation "the marker." However, dependent as it is on claims 1 and 4, the use of the term "the marker" in claim 5 clearly refers back to the marker recited in claims 1 and 4, and "the marker" is equivalent to stating "said marker" in a dependent claim. Accordingly, this ground for rejection may be withdrawn.

Claims 23-25 are rejected as being indefinite because it was asserted to be unclear how the recitations of these claims further limit the method of claim 1. These claims are herein amended to address the asserted indefiniteness. Thus, claim 23 as amended now limits claim 1 from which it depends by further requiring that the marker, "in order to be detectable, must first react with enzymes in the patient's mouth." Claim 24 as amended now limits claim 1 from which it depends by further requiring that the marker, "in order to be detectable, must first react with acids in the patient's stomach," while claim 25 as amended requires that the marker, "in order to be detectable, must first be absorbed in the patient's gastrointestinal tract and then be, at least partially, excreted from the lungs." This ground for rejection may therefore be withdrawn.

Claim 26 stands rejected as lacking antecedent basis for the term "the marker concentration." The claim is herein amended to remove the offending language.

Claim 26 is further rejected as indefinite for being unclear "how the patient's breath is analyzed to ascertain the concentration of the odorous marker." It is stated that Claim 1 relates to a method which merely defines a "yes" or "no" answer with respect to the medication having been taken or not. The Examiner kindly reviews the specification and identifies support in the specification for the determination of not only the presence or absence of the marker in the patient's breath, but also the concentration of the marker in the sample of the patient's breath. The claim as herein amended recites this determination for which the Examiner has already identified support.

Thus, the claim as amended requires only the calculation of the concentration of the marker in the sample of the patient's breath; therefore, this ground for rejection may be withdrawn.

Claim 27 is rejected because it is asserted that there is insufficient antecedent basis for the limitation "the patient's taking of the medication." Claim 27 is herein amended to reference establishment of a baseline for a patient at a time prior to a time at which the patient's compliance or otherwise is to be ascertained. Accordingly, this ground for rejection may be withdrawn.

The amendment to claim 27 also addresses the Examiner's stated concern with respect to the clarity of the recitation "prior to the patient's taking of the medication." As amended, the claim makes it clear that the time at issue is prior to the time at which the patient's compliance in taking the medication is to be ascertained.

Claims 29 and 30 stand rejected as being incomplete, with claim 29 assertedly failing to provide specific manufacturing steps for producing the medication combined with the detectable marker, and claim 30, drawn to transdermal delivery, is said to fail to further limit the method of claim 1 from which it depends as it is drawn to an intended use.

With respect to claim 29, the specific limitations directed to production of a medication are: (1) "identifying a marker substance detectable in gaseous exhaled breath" and (2) "combining a medication with said detectable marker substance." These are very specific manufacturing steps. Those skilled in the art of medication preparation would have no difficulty in following these simple, direct and clear steps or instructions included in the claimed method for producing a medication. Reconsideration and withdrawal of this ground for rejection is therefore requested.

Claim 30 is hereby amended to recite that the marker of claim 1 and the claimed method of claim 1 is to be practiced in a combination in which the medication is adapted for transdermal delivery. Accordingly, this is not a recitation of an intended use but an instruction to those skilled in the art that in order to practice the method of claim 30, the medication must include components

which facilitate transdermal delivery. Applicants urge that in light of this amendment, this ground for rejection may be withdrawn.

4. 35 USC §102(e):

Claims 1, 2, 7-9, 12-21, 23-27, 29, and 30 stand rejected as being anticipated by Katzman (5,962,335). Applicants respectfully traverse.

The Office Action states that "Katzman discloses a breath test for detection of drug metabolism. Katzman discloses that a safe and effective amount of the drug, isotopically-labelled, is administered to a subject...Katzman discloses that following the step of administering the drug to the subject, the exhaled breath of the subject is analyzed to detect a metabolite or metabolites, and subsequently the concentration of metabolite is used to determine the rate of metabolism of the drug (lines 21-36, col.7; lines 38-40, col.8)." This is correct – i.e. it is a necessary predicate of the method of Katzman that a drug is in fact administered to a subject, and this, precisely, is a key distinction between that which is disclosed and suggested by Katzman and that which is disclosed and claimed in the instant application: namely, that according to the method of the present invention, the taking of a particular drug is the unknown quantity to be determined, whereas in Katzman, there can be no doubt about this event. In fact, throughout Katzman, it is specifically disclosed that there can be no question about whether the patient has taken the drug the rate of metabolism of which is to be determined – it would make no sense whatever for this to be an unknown in the method of Katzman. Thus, see, column 2, lines 17-32; column 3, lines 16-31; column 4, lines 24-36; all of which presuppose that the drug, the metabolism of which is to be measured, has in fact been taken. This is made explicit at column 5, lines 25-27 which states: "The breath test of the present invention can be performed as follows. **First, the drug is administered to the subject. Next...**". This leaves no doubt that a necessary predicate of the Katzman method is the certainty that the drug has in fact been taken. There are six examples in the Katzman disclosure. In every one of these examples, there is an explicit reference to the need for, as a necessary predicate to subsequent testing for metabolites, the definite administration of the drug whose metabolism is to be tested:

In Example 1, column 5, lines 58-60: "Next, a safe and effective amount of the drug, preferably appropriately labelled, **is then administered to the subject.**" At column 6, lines 44-46, it is stated: "By the term "administered", it is meant that a method in accordance with good medical practice is used to introduce the drug into the subject", i.e. this is a given, not what is to be determined. At column 7, lines 13-15, it is stated: "Following the step of administering the drug to the subject, the exhaled breath of the subject is analyzed to detect a metabolite or metabolites."

In Example 2, column 10, lines 35-36: "Next, the isotopically-labelled trimethadione **is administered to the subject.**"

In Example 3, column 11, lines 39-41: "Next, the isotopically-labelled nitrous oxide **is administered to the subject**."

In Example 4, column 12, lines 10-11: "Next, the isotopically-labelled paraldehyde **is administered to the subject**."

In Example 5, column 12, lines 62-63: "Next, the isotopically-labelled cyclosporine **is administered to the subject**."

In Example 6, column 13, lines 36-38: "As another example, the breath test kit could include, in addition to the isotopically-labelled drug, **a device for administering the drug to the subject**."

The claims according to Katzman are consistent with the foregoing comments, in that, claim 1, from which all other claims depend, requires as step c: "following said measuring step, **administering said drug labelled with said non-radioactive isotope to the subject**."

Therefore, the precise thing that is desired to be determined according to the present

invention is already a required given according to the disclosure of Katzman. The absence of a metabolite detected according to the method of Katzman, therefore, would not be taken as an indication of non-compliance in taking the medication, but rather, as an indication that the medication is not metabolized – the non-taking of the medication simply having been ruled out by the fact that in the type of metabolic studies to which Katzman is directed, the non-taking of the medication is simply an unacceptable variable which must be eliminated by certainty as an initial matter that the medication has been taken. It should further be noted that, according to the method of Katzman, in order to administer the drug (API) it is necessary for a second individual (presumably a healthcare worker) to be present to administer the drug and that the individual being tested could not perform the testing outlined in Katzman by him- or herself (i.e. Katzman claims a test of enzyme metabolism which will have to be administered by a second party and would only be used on an intermittent basis; the sample would have to be collected and run on fairly sophisticated equipment by lab personnel; the subject could not carry out the analysis him/herself; therefore, there is nothing in Katzman to suggest using its methodology to test for adherence monitoring).

Aside from the foregoing distinctions, which themselves clearly distinguish the present invention from that which is disclosed or suggested according to Katzman, it should also be noted that there is no disclosure or suggestion in Katzman that an additive to a given medication might be the element to be detected, rather than the drug itself or a metabolite of the API. Thus, with respect to the present claim set in which the detectable marker is not the API itself or a metabolite thereof, there is this further reason for Katzman to fail as an anticipatory reference. This is a further significant distinction because, according to Katzman, each time a new drug's metabolism is to be tested, a newly labelled compound has to be produced. For purposes of commercial distribution of such a drug, it is costly to go through all of the regulatory procedures each time a new labelled form of an API is produced if subsequent compliance monitoring were to occur where the API itself is or contains the marker. The present invention solves this problem by permitting the marker to be either included in the API itself (see claim 2) or merely combined with the API (by difference from claim 2, see claims 1, 4-27, 29 and 30). The time and expense of having to traverse the entire regulatory approval pathway for a modified API is thus completely avoided by the present invention when the

marker is not part of the API but is merely combined with the API in the medication. There is no necessary change to the API in using the present technology. The marker, according to the present invention, can be a coating, an addition to the matrix of a capsule, pill, liquid, etc. which does not require any changes in the manufacture of the API. Markers may be chosen which do not at all modify the metabolism of the API even though the markers of the present invention may themselves undergo metabolism by pathways unrelated to those required for metabolism of the API. In contrast, Katzman, in order to monitor metabolism of the API, must monitor metabolites of the API, and is thus limited by considerations related to safety, bioavailability, manufacturing, shelf-life etc of the API itself. By contrast, according to the present invention, where the marker is not the API itself, those skilled in the art will appreciate that all of the ingredients that go into the manufacture of a pharmaceutical, aside from the API itself, may be chosen for monitoring, provided they are detectable, are non-toxic and do not interfere with the metabolism of the API. In order to emphasize and trap this aspect of the invention, new claims 31-33 are introduced.

In light of the foregoing distinctions, Applicants respectfully urge that this ground for rejection may be withdrawn.

5. 35 USC §102(b):

Claims 1, 2, 6, and 9-11 are rejected as anticipated by Forester (4,762,719). Applicants respectfully traverse.

Forester discloses a cough drop. The Office Action asserts that "smelling of the exhaled breath [of someone who has taken a Forester cough drop] would confirm or deny the presence of the detectable marker, thus showing if the cough drop had been taken or not."

Aside from the fact that Forester does not disclose or suggest that compliance or non-compliance in taking the disclosed cough drop should be achieved by smelling the breath of a person in order to make this determination, Forester as well does not disclose or suggest "obtaining a sample

of the patient's gaseous exhaled breath." Further, as herein amended, claim 1 includes the requirement of "utilizing an instrument adapted to detect said marker detectable in gaseous exhaled breath," which is neither disclosed nor suggested by Forester. As claims 2, 6, and 9-11 depend from claim 1, this rejection should be withdrawn with respect both to claim 1 and these dependent claims. Reconsideration is respectfully requested.

6. 35 USC §103:

Claims 4, 5, 7 and 8 stand rejected as being unpatentable over Forester in view of Payne (WO98/39470) and in view of Kell (5,652,146). Applicants respectfully traverse.

The deficiencies of Forester have been discussed above. Payne is cited as a disclosure of "a method of detecting conditions by analysis of gases or vapors" including use of "an array of semiconducting organic polymer gas sensors ...other types of gas sensors..." Kell is cited as a disclosure of "a method of monitoring compliance with medication prescriptions...to ensure the medication is actually being taken as required (lines 11-16, 37-41, col.1)."

The Office concedes that "Forester does not disclose analyzing the patient's breath to confirm the presence of the marker by either semiconductor gas sensor technology or conductive polymer gas sensor technology, nor by a spectrophotometer or a mass spectrophotometer." This concession is consistent with the distinction noted above in response to the anticipation rejection based on Forester. However, this concession misses the fact that Forester does not disclose detection of compliance in taking a medication at all, whether by use of sensor technology or any other means, via sampling of a patient's expired breath. This shortcoming is not cured by disclosure of Payne, which, while directed to analysis of gases or vapours from a respiring subject, neither discloses nor suggests use of such a method for measuring compliance in taking a medication. The combination of Forester and Payne with Kell, likewise does not create a valid *prima facie* case of obviousness, as Kell, while it is concerned with patient compliance in taking a medication, is directed at achieving such monitoring using urine samples, not breath samples from the patient whose compliance is to be

monitored. Thus, in combination, Forester does not in any way teach or suggest monitoring of the breath for detection of compliance; and Payne and Kell are directed to breath monitoring for detection of a condition that is unrelated to compliance with taking a medication, or to urine monitoring for compliance in taking a medication, respectively. It is thus not at all clear that one of ordinary skill in the arts relevant to Forester, Payne and/or Kell would have looked to each of these references that are combined, without first reading the present disclosure and then seeking to, in a hindsight fashion, identify separate disclosures for combining to arrive at the present method. As such, the references cited here do not come close to establishing a valid *prima facie* case of obviousness. The Supreme Court in *KSR Int. v. Teleflex Inc.*, 127 S. Ct. 1721 (2007) warned that "A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning," even though the Court found that this is not a rigid preventative rule. However, in this case, the combination of Forester (cough drop, not even disclosing or suggesting compliance monitoring), Payne (testing of disease conditions by monitoring breath) and Kell (testing compliance by monitoring urine) does not even amount to an *obvious to try* combination with respect to the present method, which monitors compliance in taking medication by monitoring breath. Forester does not suggest monitoring at all. Payne does not suggest monitoring of adherence in taking medication. Kell does not suggest monitoring breath to monitor adherence in taking prescribed medication.

Merely because claim 4 requires use of sensor technology selected from the group consisting of semiconductor gas sensor technology and conductive polymer gas sensor technology, does not mean that those skilled in the art would have been motivated to combine the Payne or Kell references with each other or with the Forester reference. Claim 5 depends from claim 4 and further requires a unique electronic fingerprint as an indication of the marker's presence in the patient's breath. Likewise with respect to the requirement of using a spectrophotometer according to claim 7, and a mass spectrometer according to claim 8. Reconsideration and withdrawal of this rejection is therefore respectfully requested.

6. 35 USC §103:

Claims 4 and 5 are further rejected as being unpatentable over Katzman in view of Payne. Applicants respectfully traverse. The deficiencies of Katzman and Payne have been discussed above. Reiterating briefly, Katzman requires, as a predicate, that a medication is definitely taken prior to initiation of metabolic studies, and, in addition, only monitors metabolites of the API. Per the present invention, it is the taking of the medication which is the unknown item to be determined, and, in addition, the marker may be combined with the API rather than being required to be present in the API itself. Directed as it is to detection of conditions unrelated to compliance with a prescribed medication regimen, Payne does not cure these defects in Katzman. Accordingly, Applicants urge that this rejection be reconsidered and withdrawn.

7. 35 USC §103:

Claim 6 is rejected as unpatentable over Katzman in view of Forester. Applicants respectfully traverse. It is unlikely that one skilled in the art would have any reason to combine these references in the absence of Applicants' teachings. The deficiencies of Katzman are discussed above. Claim 6, which depends from claim 1, requires the determination of whether a medication has been taken at all, rather than determination of whether a medication that has definitely been taken is being metabolized, and if so, how quickly. Even if one were to combine Katzman with the cough-drop patent of Forester, Forester does not cure these defects. Therefore, Applicants urge that this rejection should be withdrawn.

8. 35 USC §103:

Claim 22 is rejected as unpatentable over Forester in view of Payne and Ueda (5,425,374). Applicants respectfully traverse. Ueda is cited as a disclosure of dehumidification of an expired air sample. However, even though Ueda may disclose dehumidification of a sample, it does not cure the defects in the combination of Forester (which fails to disclose monitoring of a patient's compliance

in taking a medication using an instrument adapted to detect the detectable marker), and Payne, (which is not directed at monitoring a patient's compliance in taking a medication). Accordingly, this rejection may be withdrawn.

9. 35 USC §103:

Claim 22 is further rejected as unpatentable over Katzman in view of Payne and Ueda. Applicants again traverse. The insufficiency of the Katzman/Payne combination of references is discussed above. Ueda, even though it might disclose dehumidification of a sample, does not cure the basic defect in Katzman (which is also not cured by Payne) of failing to teach monitoring of whether a medication is taken of one's own volition (the administration of medication being, according to Katzman, a necessary given). This rejection may therefore also be withdrawn. Reconsideration is respectfully requested.

10. The Examiner's Responses to Arguments Previously Made:

Pages 15 - 17 of the latest Office Action outline reasons why Applicants' previous arguments were not considered persuasive. Though Applicants respectfully disagree, they assert that the present response provides an amended set of claims and arguments based on such amendments which clearly distinguish the claimed invention from what is taught in the cited references.

11. Conclusion:

All grounds for objection or rejection having been addressed and overcome herein by amendment of the claims and appropriate arguments in support of those amendments, Applicants urge that the currently amended claim set is in condition for allowance. No new matter has been introduced. Expedited passage of this application to patent is respectfully requested.

In the event that there are any minor issues which the Examiner believes should be addressed prior to passage of this case to allowance, it is respectfully requested that the Examiner telephonically contact the undersigned to discuss appropriate resolution of any such remaining issues.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

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